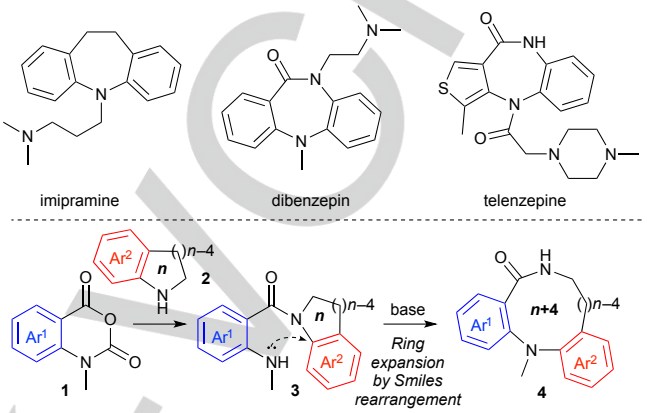
Medium-ring analogues of dibenzodiazepines by conformationally induced Smiles ring expansion

Romain Costil, Quentin Lefebvre, and Jonathan Clayden*[a]

Abstract: Analogues of dibenzodiazepines in which the 7-membered nitrogen heterocycle is replaced by a 9-12 membered ring were made by an unactivated Smiles rearrangement of 5-8 membered heterocyclic anthranilamides. The conformational preference of the tertiary amide in the starting material leads to intramolecular migration of a range of aryl rings, even those lacking electron-withdrawing activating groups, and provides a method for n→n+4 ring expansion. The medium-ring products adopt a chiral ground state with an intramolecular, transannular hydrogen bond. The rate of interconversion of their enantiomeric conformations depends on solvent polarity. Ring-size and adjacent steric hindrance enables the modulation of this 'hidden hydrophilicity', making this scaffold a good candidate for drug development.

Approaches to drug design have recently started employing shape-based 3D molecular descriptors in an effort to "escape from flatland",[1] with good success in the prediction of the likeliness of clinical success.[1b,1c] Medium-sized rings (with 8 to 12 atoms) present promising scaffolds for the development of small-molecule drugs with an extended three-dimensional shape. The limited flexibility of these rings is beneficial for enhanced binding affinity, while their well-defined conformations ameliorate physicochemical properties such as bioavailability or cell permeability.[2] Nonetheless it is well established that unfavourable transannular interactions increase the enthalpy of transition states of reactions leading to medium rings.[3] This makes their synthesis difficult,[4] and consequently medium rings are under-represented in screening libraries.[2b,5] Only recently, some medium-ring lactams have been found active against myelogenous leukemia,[6a] while trapoxins and apicidins, two classes of cyclotetrapeptides isolated from fungi, are anti-protozoal agents that function by inhibition of histone deacetylase.[6b,6c]

Dibenzodiazepine tricyclic antidepressants (TCAs, Scheme 1) are widely prescribed for the treatment of depression, schizophrenia, or nocturnal enuresis.[7] Dibenzodiazepines possess a pair of rigid but rapidly interconverting enantiomeric "butterfly" conformations, arising from the strain in the dibenzo-fused 7-membered heterocycle.[8] This interconversion is locked in telenzepine, of which one of the two atropisomers is 500 times more active than the other.[9]



Scheme 1. Prototypical tricyclic antidepressants and our approach to their medium-ring analogues.

Ring expansion provides an appealing way to make medium-sized heterocyclic rings, because transannular strain is to some extent mitigated in the transition state leading to the medium ring,[2b,10] and because heterocycles of rings sizes 5-7 are readily available. In this paper we report the use of an unconventional variant of the Smiles rearrangement[11] to generate medium rings from much simpler benzo-fused nitrogen heterocycles by n→n+4 ring expansion.[12] The work builds on our observation[13] that the usual electron-withdrawing activating substituents are not necessary for the Smiles rearrangement of tertiary anilides, because conformational preorganization[14] about the N–CO bond is sufficient to place the nucleophilic migration terminus and the electrophilic aromatic ring in close proximity. Scheme 1 shows the overall strategy, and illustrates the similarity of the reaction products to ring-expanded analogues of the biologically active dibenzodiazepines.

Anthranilamides **3** were made efficiently by condensation of isatoic anhydride derivatives **1** with nitrogen heterocycles **2** (See the Supporting Information for details).[15] Compound **3b**, for example, was obtained in one step from a mixture of N-methyl isatoic anhydride and tetrahydroquinoline in THF in the presence of a base. On treatment with NaHMDS in refluxing THF, **3b** rearranged to the migration product **4b**, having a ten-membered ring, in 40% yield (Table 1, entry 1). Increasing the temperature to 100 °C (in a sealed tube) improved the yield of the product (entry 2), but also led to decomposition to the corresponding *N*-methyl anthranilic acid and tetrahydroquinoline (THQ, Table 1, final column). Microwave heating promoted a cleaner reaction, giving the product in 72% yield after only 15 min (entry 3). KHMDS gave comparable results (entry 5), but there was negligible conversion with LiHMDS. Silazide bases seem particularly suited for this ring expansion as other bases investigated were either too weak, leaving the starting material untouched, or too nucleophilic, leading to decomposition (entry

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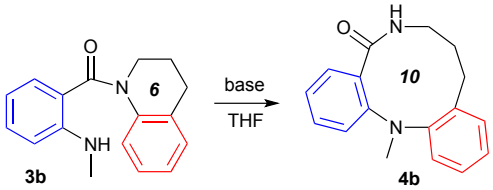
6). 2-Methyl THF provided a good alternative solvent, giving the product in 67% isolated yield (entry 4), whereas toluene and MTBE led to decomposition (see Supporting Information).

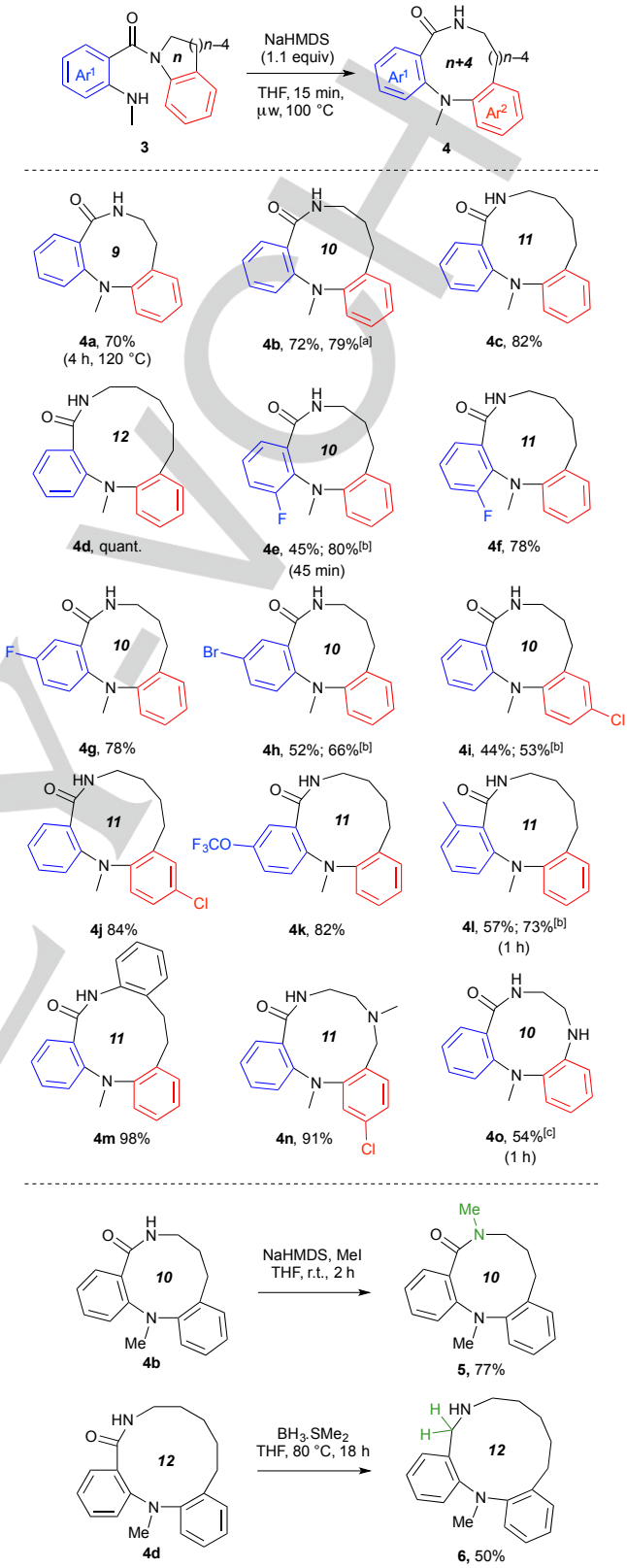
Table 1. Optimisation of the reaction conditions.



Entry	Base	T / °C	*t*	Isolated yield **4b** / %	Recovered THQ[a] /%[b]
1	NaHMDS	66	16 h	40[b]	38
2	NaHMDS	100	15 min[c]	66	22
3	NaHMDS	100	15 min[d]	72	<5
4	NaHMDS	100	15 min[d]	67[e]	<5
5	KHMDS	100	15 min[d]	62[b]	<5
6	LiHMDS	100	15 min[d]	2[b],[f]	<5

Reaction conditions: **3b** (0.11 mmol, 1.0 eq.), with base (1.1 eq.) in THF (0.2 M). [a] THQ = 1,2,3,4-tetrahydroquinoline. [b] ^{1}H NMR yields determined using 1,3,5-trimethoxybenzene as internal standard. [c] Using a sealed tube. [d] Using a microwave reactor. [e] 2-MeTHF as solvent. [f] No product obtained with Phosphazene base P_4-*t*Bu, 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TDB) or KO*t*Bu as base.

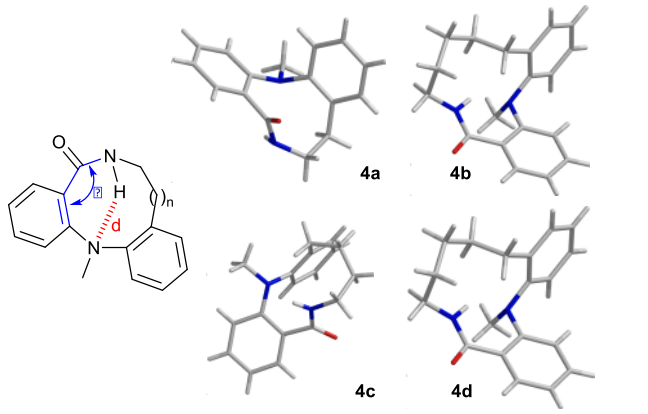
Having identified the optimal conditions for rearrangement of **4b**, we explored the scope of the reaction. Ring-expansion of the 5-membered indoline derivative **3a** required more forcing conditions (4 hours at 120 °C), but yielded the corresponding 9-membered product **4a** in excellent yield. Rearrangements of larger rings (6- to 8-membered) were even cleaner, providing the corresponding 10- to 12-membered compounds **4b-d** in excellent yields after short reaction times. The reaction showed good tolerance to halogen substituents, with fluoro-, bromo-, and chloro-substituted products **4e-j** formed without dehalogenation. The reaction conditions were fully compatible with the metabolically stable, lipophilic trifluoromethoxy group of **4k**.[16] Moderate steric hindrance around the reactive centers was tolerated, as demonstrated by products **4e**, **4f** and **4l.** Products with functionalized rings were made by rearrangement of staring materials containing alternative heterocycles. Ring opening of dibenzazepine leads to benzop-fused product **4m** in near-quantitative yield. Heterocycles containing an additional nitrogen atom, namely benzodiazepane and quinoxaline, also successfully rearranged, yielding the triaza ring systems of **4n** and **4o.**



Scheme 2. Scope of the ring expansion. Yields of isolated products. [a] 3 mmol scale. [b] Based on recovered starting material.

Further transformations of the amide function of the medium-ring products were possible. Alkylation of the amide nitrogen with methyl iodide gave **5** in 77% yield, and reduction of the carbonyl with a solution of borane dimethyl sulfide in THF, gave the more lipophilic diamine **6**.

Table 2. Crystal structures of **4a-d**, and selected structural data.



Cpd.	$d_{N\text{-}H\text{-}N}$ / Å	θ_{Ar-CO} / °	δ_{NH} / ppm	$\Delta\delta_{NH}/\%_{DMSO}$ / ppm $\%^{-1}$
4a	2.42	54	5.87	0.025
4b	2.72	58	6.46	0.031
4c	2.47	42	7.72	0.004
4d	1.95	1.3	9.10	-0.014

The conformation and dynamics of the medium-ring products were investigated in the solid state and in solution. Crystals suitable for X-ray analysis were obtained for each ring size, revealing the solid-state conformation of compounds **4a-d** and **4l** (Table 2).[17] The relative difficulty of synthesizing compound **4a** can be explained by the deviation from planarity in its amide group: the sum of the bond angles at nitrogen (344.4°) and its pyramidalization (χ_N = 47.8°) indicate significant sp^3 character at the amide nitrogen.[18] Moreover, while the C–N bond torsion angle is moderate (τ = 23.4°), the dihedral angle between the amide group and the adjacent aromatic ring (θ_{Ar-CO} = 54°) restricts delocalization.

A clear trend was observed as the ring size increased from 10 to 11 to 12. The N-H-N distance shortened from 2.72 to 1.95 Å with larger rings, with the Ar–CO dihedral angle approaching 0° in the 12-membered ring, permitting conjugation between the amide and the aromatic ring. This behavior suggested a transannular hydrogen bond, a characteristic of interest for the development of bioactive molecules with 'hidden hydrophilicity'.[5c,19]

The downfield shift of the N-H signal in the ^{1}H NMR spectra of the products **4** in $CDCl_3$ from 6.46 to 9.10 ppm with increasing ring size also indicated a progressively stronger hydrogen bond. Titration with DMSO-*d6* of solutions of compounds **4a-d** in $CDCl_3$ shifted the N-H signal in the ^{1}H NMR spectrum of 9- and 10-membered compounds **4a** and **4b** strongly downfield (Table 2, final column). Hardly any shift was observed for 11-membered compound **4c**; 12-membered compound **4d** displayed a moderate upfield shift. These observations suggest that the transannular intramolecular hydrogen bond evident in the solid state persists in solution, increasing in strength with larger rings.[20]

^{1}H NMR of compounds **4a-l** showed diastereotopic signals for the methylene groups within the ring, indicating that these heterocycles adopt chiral ground states whose enantiomeric conformations interconvert slowly on the NMR time scale.[21,22] We determined the rate constants of enantiomerisation of compounds **4a-d** and **4l** by Variable Temperature Exchange Spectroscopy (VT-EXSY), as summarized in Table 3 (See SI for details). Apart from **4a**, with its distorted amide, larger rings were significantly more flexible: 12-membered ring **4d** inverted more than 2000 times faster than 10-membered **4b** in $CDCl_3$, which may even exist as two atropisomeric enantiomers at temperatures around 0 °C. The rates to enantiomerisation were up to tenfold faster in polar solvents such as DMSO-d_6, with barriers to enantiomerisation in larger rings **4c** and **4d** being more sensitive to solvent polarity than in **4b**.

Table 3. Rates of conformational enantiomerisation of **4a-d** in various solvents.

Cpd.	Solvent	k_{enant} / s	$\Delta G^{\ddagger}$ / kJ mol^{-1} [a]	$\tau_{1/2}$ / s [b]
4a	DMSO-*d6*/CD_3OD[c]	–	–	–
	Toluene-*d8*	0.0082	84.9	42.3
4b	DMSO-*d6*	0.0074	85.1	47.1
	$CDCl_3$	0.0019	88.5	180.9
4c	DMSO-*d6*	0.16	77.5	2.1
	$CDCl_3$	0.016	83.2	21.6
4d	CD_3OD	30.7	64.5	0.011
	$CDCl_3$	4.6	69.2	0.076
4l	DMSO-*d6*	0.049	80.4	7.0
	$CDCl_3$	0.031	81.6	11.1

[a] Free energy of enantiomerisation calculated at 298 K. [b] Half-life for racemisation at 298 K. [c] Peak overlap precludes calculation in either solvent.

^{1}H NMR indicated another distinctive feature of **4a**: it exists as a pair of inequivalent diastereoisomeric conformers whose proportions vary with the solvent, with less of the minor conformer in toluene-d_8 or $CDCl_3$ (ratios of 7:1 and 6:1) than in CD_3OD and DMSO-d_6 (ratios of 3:1). Cross-peaks for the interconversion of the diastereoisomeric conformers were evident by EXSY NMR, and the barriers to their interconversion in both CD_3OD and toluene-d_8 were calculated using the Eyring equation (Table 4). While the rate at which the minor diastereomer converts to the major shows little dependence on solvent, the rate of the reverse process is strongly solvent-dependent, and is three times as fast in CD_3OD. This suggests that the major conformer owes its relative stability to an additional intramolecular hydrogen bond which is destabilised by hydrogen bonding solvents.

These diastereoisomeric conformers probably arise from the two alternative relative orientations of Ar–CO and Ar–N bonds of the adjacent secondary amide and tertiary amine groups. Clear evidence that twisting in these bonds can lead to diastereoisomeric conformers came from 11-membered ring **4l**,

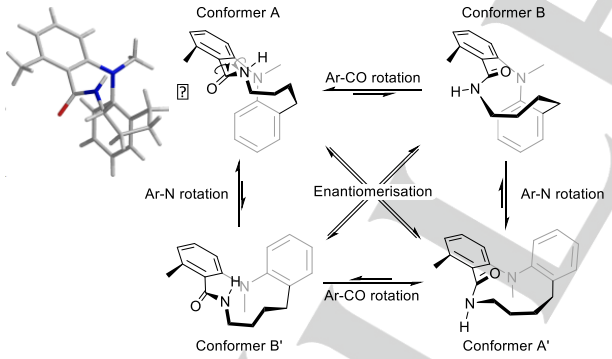
which also displays two diastereoisomeric conformers in its ^{1}H NMR spectrum.[23,24] The crystal structure of compound **4l** (Scheme 3) shows a more or less perpendicular arrangement in the amide Ar—CO bond, and a strong downfield shift of the N-H signal from 6.12 ppm in $CDCl_3$ to 7.84 ppm in DMSO-*d6* indicates that the intramolecular hydrogen bond in the ground state of **4l** is weaker than in **4c**. However, EXSY NMR shows that compound **4l** possesses a similar barrier to enantiomerisation as compound **4c**. The similarity of the rates of exchange for enantiomerisation in $CDCl_3$ and DMSO-*d6* suggests that compound **4l** adopts in solution a conformation similar to the one observed in the solid state, with a perpendicular Ar—CO bond.

^{1}H NMR of compound **4l** revealed a mixture of diastereoisomeric atropisomers in ratios of 3:1 in toluene-*d8*, 4:1 in $CDCl_3$ and 10:1 in CD_3OD. This trend, opposed to compound **4a**, shows that despite the perpendicular twist in the amide of **4l**, the flexibility of the 11-membered ring allows an intramolecular hydrogen bond in solution, but only in the minor conformer. The rate of interconversion of the diastereomers was calculated using EXSY NMR at higher temperatures (Table 4).

Table 4. Diastereomerisation parameters of compounds **4a** and **4l**.

Cpd.	Solvent	$k_{min\text{-}maj}$ [a] / s^{-1}	$k_{maj\text{-}min}$ [b] / s^{-1}	$\Delta G^{\ddagger}_{min\text{-}maj}$ [a] / kJ mol^{-1}	$\Delta G^{\ddagger}_{maj\text{-}min}$ [b] / kJ mol^{-1}
4a	CD_3OD	0.326	0.099	75.8	78.7
	Toluene-*d8*	0.306	0.035	75.9	81.3
4l	DMSO-*d6*	0.00052	0.00022	91.7	93.9
	$CDCl_3$	0.0083	0.0026	84.8	87.8

Rates and free energies of activation for conversion of [a] minor to major and [b] major to minor conformer, at 298 K.



Scheme 3. X-ray crystal structure and conformational dynamics of **4l**.

Unlike compound **4a**, diastereomerisation of compound **4l** is slower than enantiomerisation by a factor of almost 4 in $CDCl_3$ and up to 100 in DMSO-d_6. The rates of diastereomerisation of compound **4l** (unlike those of enantiomerisation) is strongly solvent-dependent. In this case, DMSO-d_6 raised the free energy of both the forward and reverse exchange relative to $CDCl_3$. Because the amide group and the adjacent aromatic ring are perpendicular in the ground state, diastereomerisation must occur through a transition state in which these two groups are coplanar. In non-hydrogen bonding solvent such as $CDCl_3$, the barrier to diastereomerisation is lowered by transient transannular hydrogen bonding between the amide proton and the diarylamine nitrogen. In DMSO-d_6, the relative energy of transition state becomes less favorable, decreasing the rate of exchange by a 10-fold. Unlike compound **4a**, for which enantiomerisation occurs through stepwise bond rotation, these higher values for diastereomerisation compared to enantiomerisation suggest that racemisation of compound **4l** occurs through geared rotation of the Ar—CO and the Ar—N bonds (Scheme 3).

To conclude, we used Smiles rearrangement of anthranilamides to yield medium-size heterocyclic analogues of dibenzodiazepines. Microwave heating reduces reaction time to 15 minutes, providing 9- to 12-membered rings in excellent yields. The reaction tolerates sensitive functional groups, and can be performed in a 'green solvent'. A transannular hydrogen bond in the products provides the structures with 'hidden hydrophilicity'. The strength of this hydrogen bond, which governs the stereodynamic properties of the medium-ring heterocycles, is modulated either by ring size or introduction of steric hindrance close to the amide group, making this class of compounds a versatile tool of drug development.

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Keywords: dibenzodiazepinone • chiral heterocycles • medium-size ring • transannular hydrogen bonding • tricyclic antidepressant

[1] (a) F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.*, **2009**, *52*, 6752; (b) D. C. Kombo, K. Tallapragada, R. Jain, J. Chewning, A. A. Mazurov, J. D. Speake, T. A. Hauser, S. Toler, *J. Chem. Inf. Model.*, **2013**, *53*, 327; (c) W. H. B. Sauer, M. K. Schwarz, *J. Chem. Inf. Comput. Sci.*, **2003**, *43*, 987.

[2] (a) A. Hussain, S. K. Yousuf, D. Mukherjee, *RSC Adv.*, **2014**, *4*, 43241; (b) L. G. Baud, M. A. Manning, H. L. Arkless, T. C. Stephens, W. P. Unsworth, *Chem. Eur. J.*, **2017**, *23*, 2225.

[3] G. Illuminati, L. Mandolini, *Acc. Chem. Res.*, **1981**, *14*, 95.

[4] For reviews, see: (a) U. Nubbemeyer, *Top. Curr. Chem.*, **2001**, *216*, 12; (b) A. Sharma, P. Appukkuttan, E. Van der Eycken, *Chem. Commun.*, **2012**, *48*, 1623.

[5] The ZINC database contains examples of azepanes, azocanes and azonanes in numbers one, three and four orders of magnitude fewer than piperidines. (a) R. D. Taylor, M. MacCoss, A. D. G. Lawson, *J. Med. Chem.*, **2014**, *57*, 5845; (b) E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.*, **2014**, *57*, 10257; (c) R. Madhavachary, E. M. M. Abdelraheem, A. Rossetti, A. Twarda-Clapa, B. Musielak, K. Katarzyna, K.-T. Justyna, T. A. Holak, A. Dömling, *Angew. Chem. Int. Ed.*, **2017**, *56*, 1.

[6] (a) G. Ding, F. Liu, T. Yang, Y. Jiang, H. Fu and Y. Zhao, *Bioorg. Med. Chem.*, **2006**, *14*, 3766; (b) S. B. Singh, D. L. Zink, J. M. Liesch, R. T. Mosley, A. W. Dombrowski, G. F. Bills, S. J. Darkin-Rattray, D. M.

Schmatz, M. A. Goetz, *J. Org. Chem*., **2002**, *67*, 815; (c) J. Taunton, J. L. Collins, S. L. Schreiber, *J. Am. Chem. Soc*., **1996**, *118*, 10412.

[7] (a) R. H. Mindham, in *Drugs in psychiatric practice*, ed. P. J. Tyrer, Butterworth-Heinemann, Oxford, **1982**, ch. 7, 177; (b) M. Rehavi, S. Maayani, L. Goldstein, M. Assael, M. Sokolovsky, *Psychopharmacology*, **1977**, *54*, 35.

[8] (a) E. W. D. Burke, G. A. Morris, M. A. Vincent, I. H. Hillier, J. Clayden, *Org. Biomol. Chem*., **2012**, *10*, 716; (b) P. W. Mui, S. P. Jacober, K. D. Hargrave, J. Adams, *J. Med. Chem*., **1992**, *35*, 201; (c) M. Simonyi, *Adv. Drug Res*., **1997**, *30*, 73; (d) K. Ramig, *Tetrahedron*, **2013**, *69*, 10783.

[9] (a) P. Eveleigh, E. C. Hulme, C. Schudt, N. J. M. Birdsall, *Mol. Pharmacol*., **1989**, *35*, 477; (b) J. Clayden, W. J. Moran, P. J. Edwards, S. R. LaPlante, *Angew. Chem. Int. Ed*., **2009**, *48*, 6398; (c) S. R. LaPlante, L. D. Fader, K. R. Fandrick, D. R. Fandrick, O. Hucke, R. Kemper, S. P. F. Miller, P. J. Edwards, *J. Med. Chem*., **2011**, *54*, 7005.

[10] Recently, the Smiles rearrangement was applied for the synthesis of precursors to dibenzoxazepinones, closely related to the dibenzazepinones: (a) F. Hu, H. Liu, J. Jia and C. Ma, *Org. Biomol. Chem*., **2016**, *14*, 11076; (b) M. O. Kitching, T. E. Hurst and V. Snieckus, *Angew. Chem. Int. Ed*., **2012**, *51*, 2925.

[11] R. Costil, H. J. A. Dale, N. Fey, G. Whitcombe, J. V. Matlock and J. Clayden, *Angew. Chem. Int. Ed*., DOI: 10.1002/anie.201706341.

[12] (a) J. E. Hall, J. V. Matlock, J. W. Ward, K. V. Gray, J. Clayden, *Angew. Chem. Int. Ed*., **2016**, *55*, 11153; (b) J. R. Donald, W. P. Unsworth, *Chem. Eur. J*., **2017**, *23*, 8780; (c) A. Borchardt, W. C. Still, *Synlett* 1995, 539; (d) T. C. Stephens, M. Lodi, A. M. Steer, Y. Lin, M. T. Gill, W. P. Unsworth, *Chem. Eur. J.* **2017**, *23*, 13314; (e) R. Mendoza-Sanchez, V. B. Corless, Q. N. N. Nguyen, M. Bergeron-Brlek, J. Frost, S. Adachi, D. J. Tantillo, A. K. Yudin, *Chem. Eur. J.* **2017**, *23*, 13319.

[13] K. Yamaguchi, G. Matsumura, H. Kagechika, I. Azumaya, Y. Ito, A. Itai, K. Shudo, *J. Am. Chem. Soc*., **1991**, *113*, 5474.

[14] R. P. Staiger, E. B. Miller, *J. Org. Chem*., **1959**, *24*, 1214.

[15] (a) F. Leroux, P. Jeschke, M. Schlosser, *Chem. Rev*., **2005**, *105*, 827; (b) F. R. Leroux, B. Manteau, J.-P. Vors, S. Pazenok, *Beilstein J. Org. Chem*., **2008**, *4*, 13.

[16] (a) S. Yamada, in *The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science*, ed. A. Greenberg, C. M. Breneman, J. F. Liebman, Wiley, New York, **2000**, ch. 8, 215; (b) Y. Otani, O. Nagae, Y. Naruse, S. Inagaki, M. Ohno, K. Yamaguchi, G. Yamamoto, M. Uchiyama, T. Ohwada, *J. Am. Chem. Soc*., **2003**, *125*, 15191; (c) F. K. Winkler, J. D. Dunitz, *J. Mol. Biol*., **1971**, *59*, 169.

[17] X-ray data has been deposited with the CCDC. Deposition numbers: **4a** 1571681; **4b** 1571682; **4c** 1571683; **4d** 1571684; **4l** 1571685.

[18] (a) J. L. Hickey, S. Zaretsky, M. A. St. Denis, S. K. Chakka, M. M. Morshed, C. C. G. Scully, A. L. Roughton, A. K. Yudin, *J. Med. Chem*., **2016**, *59*, 5368; (b) A. Whitty, M. Zhong, L. Viarengo, D. Beglov, D. R. Hall, S. Vajda, *Drug Discov. Today*, **2016**, *21*, 712; (c) P. Matsson, B. C. Doak, B. Over, J. Kihlberg, *Adv. Drug Deliv. Rev*., **2016**, *101*, 42.

[19] A. Jansma, Q. Zhang, B. Li, Q. Ding, T. Uno, B. Bursulaya, Y. Liu, P. Furet, N. S. Gray, B. H. Geierstanger, *J. Med. Chem*., **2007**, *50*, 5875.

[20] For examples of conformational studies of related chiral medium-size nitrogen heterocycles and lactams, see: (a) M. Qadir, J. Cobb, P. W. Sheldrake, N. Whittall, A. J. P. White, K. K. (Mimi) Hii, P. N. Horton, M. B. Hursthouse, *J. Org. Chem*., **2005**, *70*, 1552; (b) H. Tabata, H. Suzuki, K. Akiba, H. Takashi, H. Natsugari, *J. Org. Chem*., **2010**, *75*, 5984; (c) A. Witosińka, B. Musielak, P. Serda, M. Owińska, B. Rys, *J. Org. Chem*., **2012**, *77*, 9784; (d) B. Musielak, T. A. Holak, B. Rys, *J. Org. Chem*., **2015**, *80*, 9231.

[21] For application of a planar-chiral medium-size nitrogen heterocycle, see: K. Tomooka, C. Iso, K. Uehara, M. Suzuiki, R. Nashikawa-Shimono, K. Igawa, *Angew. Chem. Int. Ed*., **2012**, *51*, 10355.

[22] H. E. Hallam, C. M. Jones, *J. Mol. Structure*, **1970**, *5*, 1.

[23] Precedent (ref 22) suggests that the 11-membered lactam in **4l** exists exclusively as the more stable *trans* amide isomer while the smaller ring in **4a** may adopt a *cis* amide conformation.

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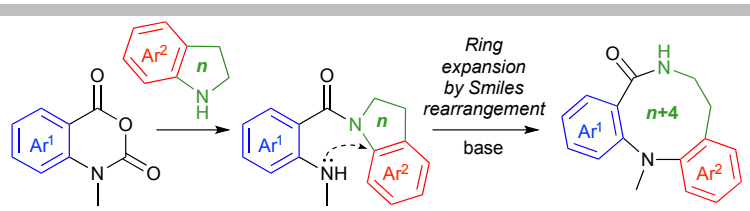

• electron-rich and -poor rings • ring sizes 9-12 • conformationally restricted products

Smiles rearrangement of readily prepared amide derivatives of benzo-fused nitrogen heterocycles requires no electronic activation to give medium ring analogues of the dibenzodiazepine tricyclic antidepressants.

Medium Ring Heterocycles

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Medium-ring analogues of dibenzodiazepines by conformationally induced Smiles ring expansion